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REMARKS

Current Office Action is non-Final

The Applicants thank the Examiner for clarifying that the current Office Action is non-Final (as indicated on the Office Action Summary page). The Examiner stated that the indication that the Office Action is Final on page 19 of the Office Action was made in error.

Formal Matters

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1-8, 10-18 and 20-23, the only claims pending and currently under examination in this application.

Claims 1-8, 10-18 and 20-23 have been amended for clarity and consistent use of terms as requested by the Examiner. Support for these amendments can be found in throughout the specification and in the original claims. Claims 1, 11 and 21 have been amended to clarify that the population is an inbred population. Support for this amendment can be found in the specification on page 3, lines 10-13 as an exemplary location. Claims 1, 11 and 21 have been amended to clarify that the computing step includes computing for each marker a ratio of first merged score to second merged score to produce a marker score, the marker score indicating at least in part a statistical distinction between whether the marker is autozygous and whether the marker is not autozygous. Support for this amendment can be found in the specification on page 19, lines 1-6. Claims 1, 11 and 21 have further been amended to include the step of examining each marker score to determine a contiguous region of markers with high sum of marker scores among contiguous regions. Support for this amendment can be found in the specification on page 19, line 20 through page 21, line 6. Claims 1, 11 and 21 have further been amended to include the step of selecting from the contiguous regions likely genetic regions for a recessive allele associated with a genetic disease or trait. Support for this amendment can be found in the specification on page 20 line 17 through page 21, line 6. Claims 1, 11 and 21 have further been amended to clarify reporting at least one of the likely genetic regions to a user of the computing device. Support for this amendment can be found in the specification on page 22, lines 13-14.

Claims 2, 4, 5, 6, 12, 14, 15, 16, 22 and 23 have been amended to be consistent with their respective base claims. Claims 10 and 20 have been amended to clarify locating a statistically significant gap in the sums of non-overlapping regions, wherein regions having sums above the gap are selected and reported to the user. Support for this amendment can be found in the specification on page 20, lines 17-23.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Objections

The dependency of Claims 10 and 20 has been corrected, as requested by the Examiner. As such, the objection may be withdrawn.

Claim Rejections – 35 USC § 101

Claims 1-8, 10-18 and 20 are rejected under 35 USC §101 as being directed to non-statutory subject matter.

Specifically, the Examiner asserts that the claims do not recite tangible expression of the identification of the region of markers, nor recite providing or outputting the result to a user.

In response, the Applicants have amended Claims 1 and 11 to include the steps of selecting regions of interest and reporting the selected regions to a user.

In view of these amendments, the Applicants submit that the claims are directed to statutory subject matter, and thus respectfully request withdrawal of this rejection.

Claim Rejections – 35 USC § 112 first paragraph – New Matter

Claims 1-8, 10-20 and 20-23 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Examiner asserts that the rejected claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill that the inventors had possession of the claimed invention at the time of

filing, introducing new matter to the instant Claims which is not supported by the specification.

In response, the Applicants have removed the claim language noted as problematic by the Examiner and amended the claims to include the following:

computing for each of said markers a ratio of said first merged score to said second merged score to produce marker scores, wherein each of said marker scores indicates at least in part a statistical distinction between whether said marker is autozygous and whether said marker is not autozygous;

examining said marker scores to determine one or more contiguous regions of markers with a high sum of marker scores;

selecting from said one or more contiguous regions of markers at least one contiguous region likely to contain a recessive allele associated with said genetic disease or trait; and

reporting said at least one contiguous region likely to contain a recessive allele associated with said genetic disease or trait to a user of said computing device.

As noted above, these amendments are fully supported by the specification and the claims as originally filed (see, e.g., pages 18 to 21).

As all of the claims as amended are directly supported by the specification, one of skill in the art understands that the inventors had possession of the claimed invention at the time of filing, and no new matter is introduced in by the instant claims. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 USC § 112 first paragraph – Enablement

Claims 1-8, 10-18 and 20-23 are rejected under 35 USC §112, as failing to comply with the enablement requirement. Specifically, it is asserted that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the relevant art to make and/or use the invention.

In making this rejection, the Examiner states that a group of people composing "the population" for estimated genotype data may be reasonably interpreted as comprising the affected people and/or their parents OR the population at large (i.e.,

unaffected population or the entire inbred population), and that as such, the method cannot be performed because calculations determining the likelihood that a homozygous allele is present more frequently than would occur randomly cannot be performed.

The claims as amended are directed to methods and an apparatus for statistical analysis of genetic data from an inbred population in which some members have a genetic disease or trait to determine regions likely to contain the allele responsible for the genetic disease or trait. As discussed below, the Applicants submit that the claimed invention is fully supported and enabled by the specification.

The Examiner asserts that the recited steps of analyzing do not compare affected and unaffected populations, and that absent such comparison, undue experimentation would be required.

In response, the Applicants respectfully submit that the claimed invention as described by the specification does not require that both affected and unaffected populations be analyzed to identify genetic regions likely to contain an allele responsible for the genetic disease or trait. As described throughout the specification, the claimed invention finds use in identifying a genetic region that is likely responsible for the genetic disease of trait in an inbred population based on statistical analyses. The basis of the statistical analyses is the concept that that such an allele is usually autozygous, i.e., an allele descended from a founder individual in the population. Using this as a basis, the claimed invention employs actual and estimated genetic analyses to identify a likely location in the genome of the allele. It is emphasized here that the claimed invention does not require the comparison of actual and estimated data from the inbred population to a distinct, non-inbred population to work.

To reiterate, the claimed invention uses statistical analyses based on an assumption that a disease-related allele is autozygous, and as such does not require actual or estimated data from another, non-inbred population.

The Examiner asserts that it is not clear what genotype data is used for determining a set of scores, referring to the rejection under 35 U.S.C. 112, second paragraph. The Applicants direct the Examiner to the Applicants' response to this

rejection under a separate heading, below.

The Office Action states that the specification does not provide guidance for how to "assign a computed function of merged scores" to markers and how to "assign a computed function to a plurality of sequential regions of markers,"

The Applicants have removed the "assigning" language from the claims and amended them to recite the step of computing for each marker a ratio of the first merged score to said second merged score to produce a marker score, the marker score indicating at least in part a statistical distinction between whether said marker is autozygous and whether said marker is not autozygous. This amendment is fully supported and enabled by the specification (see, e.g., the first five paragraphs of page 19).

It is further asserted by the Examiner that the specification does not disclose how to create or pick a plurality of sequential regions of markers from randomly picked markers, where only the markers' scores have been determined.

The Applicants submit that the human genome has been sequenced and the chromosomal positions of a very large number of human polymorphic markers are known (Please refer to the NCBI SNP Database, www.ncbi.nlm.nih.gov/projects/SNP/). As such, the relative chromosomal positions of markers are known, both at the time of selection and at the time of score determination. As such, the selection of markers having known chromosomal locations is well within the skill in the art. Furthermore, standard statistical techniques for determining error when estimating genotype frequency in a population are known in the art, as indicated on page 15, lines 12-22 of the specification. In addition, as stated in the MPEP §2163, information which is well known in the art need not be described in detail in the specification [1].

The Office Action states that the specification does not disclose how to identify a cluster of markers in response to the second assignment wherein some value is the next-to-highest value. In light of the amendments to the instant claims as discussed in

[1] *In re Buchner* 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 231 USPQ 81, 94 (Fed. Cir. 1986); and *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.* 221 USPQ 481, 489 (Fed. Cir. 1984).

detail above, the Applicants respectfully submit that the Examiner's concerns in this regard have been addressed.

It is asserted that the connection between a region of markers, a result, and a recessive disease is not disclosed by the specification, so that determining a likely region for a recessive trait would require undue experimentation.

Applicants respectfully disagree. The strength of the claimed method is that it uses assumptions based upon the facts of recessive inheritance in a small, inbred population with founder effects (i.e., the recessive allele is autozygous) to enable the cost-effective use of genomic data from a small number of individuals to determine likely loci for further characterization by sequencing. The claimed invention is drawn to selecting regions in the genome that are likely to contain the disease allele based on statistical calculations for the transmission of an autozygous allele. Once identified, the likely regions can be further characterization by routine methods, such as DNA sequencing, to determine the genetic disease or trait. As such, the claimed invention reduces the amount of resources needed to find the genetic basis of a genetic disease or trait by reducing the number of individuals who must be genotyped as well as the amount of a chromosome that must be sequenced.

The specification provides the ordinarily skilled artisan with the means to perform each and every step of the claimed method. The specification teaches the random selection of known markers in an inbred population; the genotyping of an affected family group comprising an affected individual and/or their parents; the estimation of genotype frequencies in a population of known size by genotyping (such as SNP genotyping) of a representative number of randomly chosen individuals from the population; the determination of related sampling error using straightforward statistical methods known in the art; mathematical formulae are provided for calculating in each type of individual the probability of observing a marker given autozygosity or its absence; and multiple mathematical manipulations for combining the probabilities, determine their ratio, and determining the contiguous series of markers with the highest (and next-highest) runs of scores.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[2]

As the court explained[3]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biological arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[4]

In the present case, modern high-throughput genotyping techniques routinely permit querying of many genes and SNPs at a time in an individual. Thus, given the small number of individuals required to be genotyped for the present technique and the large number of characterized human SNPs available, no more than routine experimentation is required in order to perform the genotyping of selected markers. Indeed, the inventive method reduces the amount of experimentation required to identify promising regions for sequencing.

The Examiner compares the present method to Arbour et al., Kruglyak et al. and Puffenberger et al., of record, asserting that because these representative references recite comparing two distinct populations, the claimed method, in which a single inbred population is being examined, is not enabled.

In response, the Applicants submit that the asserted fact that intra-population

[2] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[3] *In re Wands* 8 USPQ 2d at 1404
[4] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

genomic analyses are not expressly disclosed in the art of record is irrelevant to whether the claimed invention is enabled because the present application enables just such analyses, as discussed in detail above.

Therefore, the Applicants submit that the specification provides the ordinarily skilled artisan with the means to perform each and every step of the claimed invention.

The Examiner notes that the specification provides no working examples.

MPEP 2138.05 states that reduction to practice may be an actual reduction or a constructive reduction to practice. The constructive reduction to practice constituted by the present application directly provides formulae and detailed instructions for arriving at a statistical prediction of regions with an elevated likelihood of containing the locus of a recessive disease or trait. Accordingly, the specification amply fulfills the constructive reduction to practice of the present invention.

The Examiner asserts that in order to practice the claimed invention, one skilled in the art must randomly select genotype data and must guess which data to use for analyzing and determining scores.

The Applicants respectfully submit that the random selection of markers does not constitute "guessing." The selection of human SNPs from sources such as the database described above is straightforward and provides sequences which are then readily genotyped in a small number of individuals. The user may decide which genomic regions are to be assayed, ranging from a specific region of a chromosome to the entire genome. This will be determined by the user based on information that is specific to the analysis being done, as certain genetic aspects of a genetic disease or trait may be know beforehand. However, regardless of the amount of previously obtained genetic information, the claimed invention is fully enabled.

In summary, the Applicants submit that the specification amply fulfills the enablement requirements of 35 USC § 112, and as such, respectfully request withdrawal of this rejection.

Claim Rejections – 35 USC § 112 second paragraph

Claims 1-8 ,10-18, 20 and 22-23 are rejected under 35 USC §112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that because it is unclear for what population genotype data is being obtained, the instant claims are rendered indefinite.

The Applicants submit that the claims as amended recite obtaining actual genotype data from members of an inbred population having a genetic disease or trait in an inbred population and/or their parents, and obtaining estimated genotype data for the population.

As such, the indefinite language has been corrected and withdrawal of the rejection is respectfully requested.

The Examiner asserts that the method steps do not achieve the goal recited in the preamble, because there is no indication that the identified region of markers is connected to a recessive genetic disease, and thus, the intended relationship between the preamble and the method steps is unclear.

The amended claims recite selecting from said marker scores to identify likely genetic regions for a recessive allele associated with a genetic disease or trait. Accordingly, the amended claims clearly point out the intended relationship between the preamble and the subsequent method steps.

The Examiner states that the recitation in Claim 1 of "estimated genotype data" makes the claim vague and indefinite because it is unclear from the claims and specification what genotype data are estimated for.

The Applicants submit that the specification states on page 3, lines 3-8 that:

> One embodiment of these techniques includes the steps of obtaining actual genotype data for one or more affected people with the genetic disease or trait in a population and/or actual genotype data for their parents, obtaining estimated genotype data for the population, and analyzing the actual and estimated genotype data to find a region in the genome of the affected people that includes markers exhibiting particular homozygous pairs of alleles more frequently than would occur randomly.

The specification further states on page 15, lines 12-22 that:

> In step 32, estimates are obtained of genotype frequency data for the entire inbred population to which the affected persons and their parents belong. When determining these estimates, it can be assumed that the alleles a child gets for any marker from his or her parents are independent.
>
> In one embodiment, the estimates are found by actually genotyping a subset of the population. An error rate e for the estimates can be assumed, with the presence of the error indicating that a measured value in the genotyping is a result of a random selection from the population. Standard statistical techniques can be used to determine the error rate e from the size of the subset and the size of the overall population under consideration. Other techniques can be used to find the estimates without departing from the invention.

On page 16, lines 5-20, referring to Figure 4, the specification details the probability calculations used to determine the likelihood of allelic observation given assumptions of autozygosity/non-autozygosity for each family member. Line 8 indicates that n= a number of alleles possible for the marker under consideration, designated A, B, C. At line 10, the specification states that p_X is the estimated frequency of allele X in the inbred population, where X is one of alleles A, B, C. Accordingly, the allele frequencies used in calculating likelihood of observation in the affected members are the same alleles whose frequency is estimated in the inbred population.

Therefore, the Applicants submit that one of skill in the claime term "estimated genotype data" is clear and definite.

The Examiner cites several instances in Claims 1 and 11 of limitations using the phrases "assignment," "computed function," "analyzing," "being responsive to said steps of ... assigning," "substantially at least the next-to-highest," "a score" and "a marker."

In light of the amendments to the instant claims in the present response, the Applicants consider that the Examiner's concerns to have been addressed.

The Examiner asserts that with regard to Claims 1 and 11, it is not clear whether the limitation "the genotype data relative to each person for which actual genotype data

was determined" is related to the actual, the estimated, or both genotype data. The Applicants submit that the instant claims as amended recite "said genotype data," thereby indicating the use of both the actual and estimated genotype data.

Given the amendments to the claims and discussion above, the Applicants submit that the instant claims and specification fulfill the requirements of 35 USC 112, second paragraph. Withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC § 103

The Examiner rejects Claim 21 under 35 U.S.C. § 103(a) as being unpatentable over Arbour et al., *Human Mol. Genet.*, 6(5):689-694 (1997), in view of Puffenberger et al., US 2005/0158754.

The Applicants have amended Claim 21 to recite the limitations of Claims 1 and 11 (i.e., the computing, examining, selecting, and reporting steps), which have not been rejected in by the Examiner under this heading. Indeed, the Examiner notes that the Applicants have overcome the rejection of Claims 1 and 11 over the same cited art in the previous response based on the amendments.

The Applicants submit that the claim as amended is patentable over the cited art for at least the reasons provided below.

First, Arbour et al. neither teaches nor suggests a ratio of a score under an assumption that the marker is autozygous to a score under an assumption that the marker is not autozygous, nor a sum of a sequential set of the ratios. Rather, in Arbour et al., "the criterion for significant linkage was considered to be a LOD score of 3.0 or greater" (Arbour et al., page 693, left column).

Arbour et al. does not teach or suggest any combinations of the recited ratios in any way. Arbour et al. also does not appear to show any operation at all on a region of markers.

The Examiner has failed to establish that Puffenberger et al. remedies any of these deficiencies in the teachings of Arbour et. al.

As such, the combined references fail to teach or suggest all of the limitations of the present claims. Accordingly, the Applicants respectfully request withdrawal of this rejection.

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CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Timothy Joyce at (408) 553-2510.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10050845-1.

Respectfully submitted,

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